II. REMARKS

Formal Matters

Claims 1-38 are pending after entry of the amendments set forth herein.

Claims 1-6, 23, 24, 28 and 31 were examined and were rejected. Claims 7-22, 25-27, 29, and 30 were withdrawn from consideration.

Claims 1, 23, 28, and 31 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1, 23, 28, and 31 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: paragraphs 0043, 0045, 0046, 00215, and 00216. Accordingly, no new matter is added by these amendments.

Claims 32-38 are added. Support for new claims 32-38 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: claim 32: paragraphs 00143, 00150, 00164, 00166; and claims 33-38: paragraph 00231. Accordingly, no new matter is added.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Objections to the specification

The Office Action objected to the specification. The Office Action stated that paragraph 00233 states "four groups" when only three forms are listed. The Office Action further stated that trademarks were used in paragraph 00140, and that trademarks should be capitalized and be accompanied by generic terminology.

Applicants respectfully request entry of the above-noted amendments to the specification, which adequately address the objections to the specification.

Rejection under 35 U.S.C.§112, second paragraph

Claim 1 was rejected under 35 U.S.C.§112, first paragraph, as allegedly incomplete.

The Office Action stated that claim 1 omits essential steps.

Without conceding as to the correctness of this rejection, and solely in the interest of expediting prosecution, claim 1 is amended to recite "administering to the individual an agent that reduces ~~reducing~~ formation of a neurotoxic carboxyl-terminal truncated form of apoE in a neuron in the individual, wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE, and wherein formation of neurofibrillary tangles is inhibited."

Applicants submit that the rejection of claim 1 under 35 U.S.C. §112, second paragraph has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C.§102(b)

Claims 1-6 and 28 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by WO 98/01101. Claims 23 and 24 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by U.S. Patent No. 5,610,297 ("the '297 patent"). Claim 31 was rejected under 35 U.S.C.§102(b) as allegedly anticipated by Tolar et al. ((1999) *J. Neurosci.* 19:7100-7110; "Tolar").

Comments regarding the instant invention

The instant invention relates to methods of reducing the level of, and inhibiting formation of, neurotoxic carboxyl-terminal truncated apoE in a neuron in an individual. Applicants made the observation that carboxyl-terminal truncated forms of apoE induce formation of neurofibrillary tangle-like structures in neuronal cells. Such carboxyl-terminal truncated forms of apoE are neurotoxic. Reducing formation of carboxyl-terminal truncated apoE reduces the formation of such structures, and provides a means of treating disorders such as Alzheimer's Disease.

Claims 1-6 and 28 over WO 98/01101

The Office Action stated that WO 98/01101 claims a method of treating conditions associated with apoE toxicity, comprising administering a protease inhibitor, including antipain, to interfere with the production of neurotoxic fragments of apoE4. Applicants respectfully traverse the rejection.

WO 98/01101 neither discloses nor suggests methods involving reducing formation of carboxyl-truncated apoE fragments.

WO 98/01101 neither discloses nor suggests a method of inhibiting formation of neurofibrillary tangles in an individual, the method comprising administering to the individual an agent that reduces

formation of a carboxyl-terminal truncated form of apoE in a neuron in the individual.

WO 98/01101 states: "the present invention is a new method for treating a mammal having a condition associated with toxicity of whole apolipoprotein E or apoE cleavage fragments containing residues 130-169" and states that the method comprises administering a compound that "interferes with production of the toxic fragment or interferes with the receptor-binding site associated with residues 130-169 of the apolipoprotein E molecule." WO 98/01101, page 6, lines 7-14.

WO 98/01101 focuses on a region of apoE from amino acids 130-169. WO 98/01101 states that the 130-169 region is an apoE receptor binding site, and states that the 130-169 region is contained on whole apoE and on a 22 kD fragment. WO 98/01101, page 7, lines 29-33. WO 98/01101 further states that charged amino acid residues within the 141-149 domain make a significant contribution to apoE peptide toxicity. WO 98/01101, page 11, lines 30-31. WO 98/01101 states that the 22 kD thrombin cleavage fragment of apoE is neurotoxic, and can be used to assess the efficacy of test compound. WO 98/01101, page 13, lines 30-34. WO 98/01101 discusses an assay to test for inhibition of neurotoxicity of the 22 kD fragment, which assay involves treating neuronal cells *in vitro* with a test agent and 22 kD fragment, and determining the effect of the test agent on inhibition of neurotoxicity of the 22 kD fragment. WO 98/01101, Example 2, page 14, lines 16-31.

However, there is evidence in the instant application that the 22 kD thrombin cleavage fragment of apoE is not neurotoxic. Instead, the instant application provides evidence that carboxyl-terminal truncated apoE fragments that lack amino acids 244-260 are <u>not</u> neurotoxic. Specification, paragraphs 00215 and 00216; and Figure 3B. The 22 kD thrombin cleavage fragment of apoE consists of amino acids 1-191 of apoE. Thus, the 22 kD thrombin cleavage fragment lacks amino acids 244-260 identified in the instant application as essential for neurotoxicity. These data indicate that, in contrast to the assertion in WO 98/01101, the presence of amino acids 130-169 is not critical for neurotoxicity.

In addition, there is evidence in the art that peptides corresponding to the apoE receptor binding site are <u>neuroprotective</u>, not neurotoxic. See, *e.g.*, Aono et al. ((2003) *Neurosci.* 116:437-445; "Aono"; a copy of which is provided herewith as Exhibit 1). Aono reports that a peptide derived from the receptor binding region of apoE (residues 133-149) completely suppressed neuronal cell death and calcium influx associated with N-methyl-D-aspartate exposure, and that this peptide is thus

neuroprotective. Aono, Abstract. Aono discusses the contrast in the observation with the report in Tolar that the 22 kD apoE thrombin cleavage fragment is neurotoxic, states that Tolar used a peptide comprised of tandem repeats of residues 141-149, and showed neuronal cell death upon exposure to this peptide. Aono et al., page 444, column 1, second paragraph. A peptide containing tandem repeats of residues 141-149 is an artificial construct made in the laboratory, and does not exist *in vivo*. Aono further states that the tandem repeat may not be a biologically relevant model of the intact apoE protein. Aono et al., page 444, column 1, second paragraph.

The Office Action stated that while WO 98/01101 is silent with respect to apoE(Δ272-299), it does not exclude apoE4(Δ272-299) as a possible toxic fragment of apoE4, thus meeting the limitations of claim 6. However, that a reference "does not exclude" a feature is not the correct legal standard for anticipation. It is basic patent law that in order to anticipate a claim, a reference must teach each and every element of the claim. *Verdegaal Bros. v. Union Oil of California*, 2USPQ2d 1051, 1053 (Fed. Cir. 1987). Because WO 98/01101 does not disclose or suggest a method of inhibiting formation of neurofibrillary tangles, comprising administering an agent that reduces formation of neurotoxic carboxyl-terminal truncated apoE, WO 08/01101 cannot anticipate the instant invention as claimed.

WO 98/01101 does not specifically disclose or suggest the use of serine protease inhibitor to reduce formation of carboxyl-terminal truncated apoE.

WO 98/01101 states that a protein inhibitor mixture, which mixture includes a serine protease inhibitor, a cysteine protease inhibitor, and an aspartic protease inhibitor. WO 98/01101, page 15, Example 5. There is no specific disclosure in WO 98/01101 to use a serine protease inhibitor to reduce formation of neurotoxic carboxyl-terminal truncated apoE.

WO 98/01101 is not an enabling disclosure.

WO 98/01101 states that the 22 kD thrombin cleavage fragment of apoE is neurotoxic *in vitro*. WO 98/01101, page 13, lines 30-34. However, as discussed above, later publications have shown that the fragment discussed in WO 98/01101 is not toxic toward neuronal cells, as asserted in WO 98/01101. Because this fragment is not toxic, inhibiting its formation would not be expected to be a treatment for AD. Accordingly, WO 98/01101 is not an enabling disclosure. As stated in MPEP§2121, a prior art reference must be operable and enabling to be properly cited under 35 U.S.C.§102.

Notwithstanding the above discussion, and solely in the interest of expediting prosecution, claims 1 and 28 are amended to recite "wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE." WO 98/01101 neither discloses nor suggests a method of inhibiting formation of neurofibrillary tangles, comprising administering an agent that reduces formation of neurotoxic carboxyl-terminal apoE, wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE. Accordingly, WO 98/01101 cannot anticipate claims 1-6 and 28.

Claims 23 and 24 over the '297 patent

The Office Action stated that the '297 patent discloses a class of peptide α-ketoamides which selectively inhibit serine proteases, and teaches the use of these serine proteases as neuroprotectants and therapeutics for the treatment of neurodegeneration and stroke. Applicants respectfully traverse the rejection.

The '297 patent states that certain ketoamides discussed therein that are calpain inhibitors, i.e., are **cysteine** protease inhibitors, are useful as neuroprotectants and can be used as therapeutics for the treatment of neurodegeneration and stroke ('297, column 1, lines 37-42). The '297 patent does not disclose or suggest that serine protease inhibitors are useful for inhibiting formation of neurofibrillary tangles. Accordingly, the '297 patent cannot anticipate claims 23 and 24.

Claim 31 over Tolar

The Office Action stated that Tolar discusses a method of using a protease inhibitor cocktail to attenuate the production of neurotoxic apoE4 fragments in dissociated chick sympathetic neurons. Applicants respectfully traverse the rejection.

Tolar neither discloses nor suggests methods involving reducing formation of carboxyl-truncated apoE fragments.

Tolar neither discloses nor suggests a method of reducing the level of neurofibrillary tangles in a cell, the method comprising contacting the cell with an agent that reduces activation of an enzyme that catalyzes formation of a neurotoxic, carboxyl-terminal truncated form of apoE in the neuron.

Tolar neither discloses nor suggests neurotoxic carboxyl-terminal truncated apoE.

Tolar discusses formation of a 22 kD apoE fragment. Tolar, Abstract; page 7102, column 1, first paragraph under "Results." Tolar states that exposure of neurons to full-length apoE resulted in the

appearance of lower molecular weight fragments of apoE, including a 22 kD fragment, "which most likely represents the major N-terminal fragment of apoE." Tolar, column 1, first paragraph under "Results." As discussed above, the 22 kD major N-terminal fragment of apoE lacks amino acids 244-260 which were shown in the instant specification to be important for neurotoxicity of carboxyl-terminal truncated apoE. Nowhere does Tolar disclose or suggest inhibition of formation of a neurotoxic carboxyl-terminal truncated apoE fragment. Accordingly, Tolar cannot anticipate claim 31.

Tolar neither discloses nor suggest a method of reducing activation of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE and that is activated by Aβ1-42.

Tolar only discusses the use of a mixture of proteases, which mixture includes serine protease inhibitors, cysteine protease inhibitor, and aspartic protease inhibitor. Nowhere does Tolar disclose or suggest use of an agent that reduces activation of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE. Accordingly, Tolar cannot anticipate claim 31.

Notwithstanding the above discussion, and solely in the interest of expediting prosecution, claim 31 is amended to recite "wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE." Tolar neither discloses nor suggests a method of reducing the level of carboxyl-terminal truncated apoE in a neuronal cell, the method comprising administering an agent that reduces activation of an enzyme that catalyzes the formation of neurotoxic carboxyl-terminal apoE in a neuronal cell, wherein the enzyme is activated by $A\beta_{1-42}$, and wherein the carboxyl-terminal truncated apoE comprises amino acids 244-260 of apoE. Accordingly, Tolar cannot anticipate claim 31.

Conclusion as to the rejections under 35 U.S.C.§102(b)

Applicants submit that the rejections of the claims discussed above under 35 U.S.C. §102(b) have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL217.

Respectfully submitted,
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Date: May 21, 2003

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